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Brief Communication

Poor sleep quality and silent markers of cerebral small vessel disease: a population-based study in community-dwelling older adults (The Atahualpa Project)

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ABSTRACT

Background/Objectives: Evidence of a relationship between non-breathing-related sleep symptoms and silent markers of cerebral small vessel disease (SVD) is scarce. The present study aimed to evaluate this association in older people living in rural Ecuador, where the burden of stroke is on the rise.
Methods: A group of Atahualpa residents, aged ≥60 years, were interviewed with a validated Spanish version of the Pittsburgh Sleep Quality Index, and underwent magnetic resonance imaging (MRI) for identification of silent markers of SVD. Using multinomial logistic regression analysis, after adjusting for demographics and cardiovascular health status, it was evaluated whether sleep quality is associated with the severity of white matter hyperintensity (WMH), lacunar infarcts, and deep microbleeds.
Results: Out of 311 people aged ≥60 years, 237 (76%) were enrolled into the study. Mean age was 70 ± 8 years, 59% were women, 83% had primary school education only, and 73% had a poor cardiovascular health status. Seventy-eight (33%) had poor sleep quality. The MRI showed: WMH in 154 (65%) participants (moderate-to-severe in 52); silent lacunar infarcts in 28 (12%); and deep microbleeds in 17 (7%). Poor sleep quality was associated with WMH presence (OR 2.44, 95% CI 1.26 to 4.71, $p = 0.008$) and severity (β coefficient 0.77, SE 0.37, $p = 0.037$), but not with silent lacunar infarcts or deep microbleeds.
Conclusions: The present study showed an association between poor sleep quality and WMH severity. Further longitudinal studies would help to elucidate the cause and effect of this relationship.

1. Introduction

Owing to increased life expectancy and changes in lifestyles, the prevalence rates of sleep disorders and stroke are on the rise in many low-income and middle-income countries [1–3]. There is also growing evidence that links both conditions, but most studies have focused on cerebrovascular correlates of obstructive sleep apnea [4–6] and little attention has been given to other sleep-related symptoms [7]. In addition, no study has systematically evaluated the relevance of the association between these symptoms and all the silent markers of cerebral small vessel disease (SVD). This is of particular interest as SVD is a rather common pathogenetic mechanism that underlies stroke and vascular cognitive impairment in some of these regions [8]. Detection of persons at risk of developing these adverse vascular outcomes – beyond those with traditional risk factors – is important for the implementation of cost-effective preventive strategies.

The Atahualpa Project is an ongoing population-based study designed to reduce the increasing burden of non-communicable diseases in rural Ecuador [9]. Preliminary findings from the present cohort suggested an association between poor sleep quality with cardiovascular risk factors [10] and between short sleep duration with overt stroke [11]. It was hypothesized that non-breathing-related sleep symptoms are also associated with silent SVD; this study was conducted to assess the actual magnitude of the problem.

2. Methods

The Institutional Review Board of Hospital-Clínica Kennedy, Guayaquil, Ecuador (FWA 00006867) approved the protocol and the written

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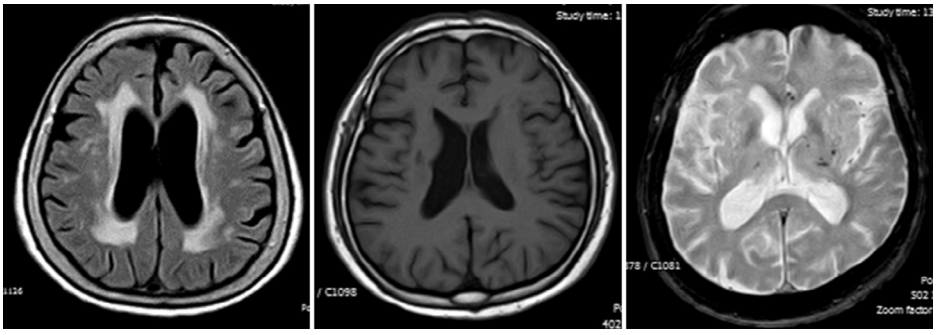

Fig. 1. Silent markers of cerebral small vessel disease on MRI. *From left to right*: severe white matter hyperintensities of presumed vascular origin (fluid-attenuated inversion recovery – TR 9000, TE 120, TI 2500), lacunar infarct in right subcortical white matter (T1-weighted – TR 594, TE 15), and deep microbleeds (gradient-echo – TR 686, TE 23). Images correspond to three different people aged ≥60 years.

informed consent. Atahualpa is a village that is representative of the rural coastal areas of Ecuador. More than 95% of the population belongs to the Native/Mestizo ethnic group (Amerindians) and their living characteristics have been detailed elsewhere [9].

All Atahualpa residents aged ≥60 years were identified during a door-to-door survey and invited to participate in the study. During the survey, trained rural doctors interviewed consenting individuals with field instruments directed at assessing demographics, vascular risk factors and sleep quality. Enrolled participants with no contraindications were then transported to Guayaquil for magnetic resonance imaging (MRI) neuroimaging evaluation.

2.1. Vascular risk factors

The cardiovascular health (CVH) status was evaluated by the use of the seven metrics proposed by the American Heart Association, including: smoking status, body mass index, physical activity, diet, blood pressure, fasting glucose, and total cholesterol blood levels. Each metric was categorized as ideal, intermediate or poor, and the CVH status was classified as poor if at least one metric was in the poor range [12]. To recognize people with overt strokes, rural doctors screened all persons with the use of a validated field questionnaire, and then certified neurologists confirmed the diagnosis, as previously described [13].

2.2. Sleep quality investigation

A validated Spanish version of the Pittsburg Sleep Quality Index was used [14]. This questionnaire evaluates symptoms in the previous month and consists of 18 questions assessing: sleep duration, sleep disturbances, sleep latency, days of dysfunction due to sleepiness, sleep efficiency, overall sleep quality, and any medications needed to sleep (maximum score is 21 points). The cutoff value for poor sleep quality is ≥6 points.

2.3. Imaging protocol

All studies were performed with a Philips Intera 1.5T (Philips Medical Systems, the Netherlands) at the Hospital-Clínica Kennedy. The MRI included two-dimensional multi-slice turbo spin echo T1-weighted, fluid attenuated inversion recovery (FLAIR), T2-weighted, and gradient-echo sequences in the axial plane, as well as a T1-weighted sequence oriented in the sagittal plane. The pre-established brain-imaging package, delivered by the manufacturer to assure uniformity of the data, was used. Slice thickness was 5 mm, with a 1 mm gap between slices.

The MRIs were independently interpreted by an experienced neurologist (OHD) and a neuroradiologist (JL), who were blinded to clinical data. Inter-rater agreement was assessed for all findings, and disagreements were resolved by consensus. Interest focused on the presence of silent markers of SVD. These included white matter hyperintensity (WMH), lacunar infarcts, and deep microbleeds (Fig. 1). The WMH were defined as lesions appearing as hyperintense on T2-weighted images that remained bright on FLAIR (without cavitation) and were graded according to the modified Fazekas scale [15]. Lacunar infarcts were defined as fluid-filled cavities measuring 3–15 mm located in the territory of a perforating arteriole [16]. Deep microbleeds were identified and rated according to the microbleed anatomical rating scale (MARS) [17].

2.4. Statistical analyses

Descriptive statistics were presented as means with standard deviations for continuous variables and as percentages with 95% confidence interval (CI) for categorical variables. Kappa statistics were used to assess inter-rater agreement. To evaluate the association between silent markers of SVD and sleep quality, a multinomial logistic regression analysis was performed with WMH, lacunar infarcts, and deep microbleeds as the outcomes; sleep quality as the exposure; and confounders (age, sex, education, and CVH status) as the independent variables. Statistical analyses were carried out by using STATA version 13 (College Station, TX, USA).

3. Results

Out of the 311 Atahualpa residents aged ≥60 years, 258 (83%) underwent MRI. The reasons for not obtaining MRI included: refusal to participate ($n = 26$), severe disability ($n = 11$), claustrophobia ($n = 8$), and an implanted pacemaker ($n = 1$); seven additional people had died or emigrated between the survey and the invitation. Twenty-one of the 258 people were further excluded because of a clinical diagnosis of overt stroke.

The mean age of the 237 participants was 70 ± 8 years, 140 (59%) were women and 196 (83%) had primary school education only. A poor CVH status was noticed in 172 (73%) participants, with a mean of 1.2 ± 1 poor metrics per person. Seventy-eight (33%) had poor sleep quality. Kappa coefficients for inter-rater agreements ($n = 237$) of MRI lesions of interest were 0.88 for WMH, 0.86 for lacunar infarcts, and 0.76 for deep microbleeds. After consensus, 154 participants (65%) had WMH, which were moderate-to-severe in 52. Silent lacunar infarcts were noticed in 28 (12%) cases, and deep microbleeds in 17 (7%).

Participants with poor sleep quality were older than those with good sleep quality (72.5 ± 10 vs 68.6 ± 6.7 years, $p = 0.001$), but when both groups were compared, there were no differences in the other independent variables. Some of the independent variables

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Table 1
Studies evaluating the association between non-breathing-related sleep disorders and silent markers of cerebral small vessel disease on magnetic resonance imaging.

Author [reference]	Number of participants	Study design/ setting	Sleep assessment	Outcomes on MRI	Variables used for adjustment	Results
Kanda et al. [19]	136	Cross-sectional. Community-dwelling older people in Onagawa (rural Japan)	Insomnia, difficulty falling asleep, early awakening (<05:00)	WMH (visual rating); silent strokes	Age, sex	Association of early awakening with WMH ($p = 0.03$). No association with silent strokes.
Cheng et al. [20]	72	Cross-sectional. Outpatients with vascular dementia in Taipei (Taiwan)	20-item SDQS	WMH (visual rating)	Age, sex, depression	Association of SDQS scores with WMH ($p = 0.004$).
Alosco et al. [21]	53	Cross-sectional. Patients with heart failure in Akron, Ohio (USA)	Pittsburgh Sleep Quality Index	WMH (volumetric assessment)	Age, left ventricular function, diabetes, sleep apnea, hypertension, depression	Association of poor sleep quality with WMH ($p = 0.046$).
Ramos et al. [22]	1244	Cross-sectional. Multiethnic population in Northern Manhattan, NY (USA)	Nightly sleep hours (single question)	WMH (volumetric assessment)	Age, race, education, insurance status, obesity, smoking, alcohol, diabetes, hypertension, cardiac disease	Association of long sleep duration (≥9 h) with WMH ($p = 0.035$).
Present study	237	Cross sectional. Community-dwelling older people in Atahualpa (rural Ecuador)	Pittsburgh Sleep Quality Index	WMH (visual rating); silent strokes; deep microbleeds	Age, sex, education, cardiovascular health status (smoking, body mass index, diet, physical activity, blood pressure, fasting glucose, total cholesterol)	Association of poor sleep quality ($p = 0.037$) with WMH. No association with silent strokes and deep microbleeds.

MRI, magnetic resonance imaging; WMH, white matter hyperintensity; SDQS, sleep disturbance symptoms questionnaire.

influenced outcomes (SVD markers). Participants with moderate-to-severe WMH were: older (77.9 years ± 7.9 vs 69.7 years ± 7.5 vs 65.2 years ± 4.3, $p = 0.0001$); less educated (98% vs 86% vs 59%, $p = 0.0002$); and had a trend for having poor CVH status (81% vs 77% vs 53%, $p = 0.07$) when compared to those with mild and with no WMH, respectively. Silent strokes were significantly associated with age (74.5 years ± 6.9 vs 69.7 years ± 8.1, $p = 0.001$) and non-significantly with poor CVH status (86% vs 71%, $p = 0.09$). Deep microbleeds were not associated with any of the independent variables.

Poor sleep quality was associated with WMH presence (OR 2.44, 95% CI 1.26 to 4.71, $p = 0.008$) and severity (β coefficient 0.77, SE 0.37, $p = 0.037$), but not with the presence of silent lacunar infarcts (OR 1.2, 95% CI 0.5 to 2.8) or deep microbleeds (OR 1.01, 95% CI 0.96 to 1.09), after adjusting for all the independent variables.

4. Discussion

The main findings of this population-based study provide robust evidence for a direct association between poor sleep quality with WMH severity. White matter hyperintensity was visually rated, and this could be perceived as a potential limitation of the study. However, the Fazekas scale and volumetric assessment provide near-equivalent estimates of WMH severity and can be used almost indistinctly [18]. Poor sleep quality may be a reflection of the interaction between non-breathing and breathing-related sleep symptoms together with the presence of systemic diseases. In the present study, the statistical models used for assessing the relationship between sleep quality and silent markers of SVD were adjusted for the complete set of cardiovascular risk factors proposed by the American Heart Association [12], reducing the possibilities that a non-sleep-related confounding variable accounted for the observed associations.

The complex relationship between sleep-related disorders and silent markers of SVD is probably bidirectional, but the information is scarce. To get more insights about this subject, two of the authors (OHD, PC) independently conducted a PubMED search up to July 2014, using the keyword 'sleep' combined with 'white matter', 'small vessel' or 'silent stroke'. After consensus, the search revealed four studies that had investigated the association between non-breathing-related sleep disorders and silent markers of SVD in cross-sectional designs [19–22]. All of them found an association between sleep duration or sleep quality with WMH severity, but the single study that also evaluated silent strokes did not find an association (Table 1). Two of the studies suggested that sleep problems might affect the subcortical white matter through changes in cerebral blood perfusion [21,22]. In the other two, however, it was hypothesized that SVD-related brain damage causes sleep-related symptoms through the disruption of periventricular fibers connecting the frontal lobes with structures deep in the brain such as basal ganglia and hypothalamus [19,20].

While in the present study causality could not be assessed, the fact that only moderate-to-severe WMH were associated with poor sleep quality might suggest that sleep symptoms are a consequence of a diffuse subcortical and periventricular damage. Should the poor sleep quality be the cause of SVD, an association with all silent markers of SVD would have been found. A single, longitudinal study provided further support for this hypothesis, as hypertensive patients ($n = 932$) were evaluated with MRI and followed-up for one year. In that cohort, short-sleep and long-sleep durations related to incident-overt strokes only in people who already had a silent stroke, but not in those who were stroke-free at baseline [23]. This suggests that sleep disturbances were not causally related to stroke occurrence but that people who already had this silent marker of SVD were more prone to develop both overt strokes and sleep disorders.

In conclusion, the present study revealed an association between poor sleep quality and severity of WMH. Further longitudinal studies in this population would help to clarify the cause and effect of this relationship.

Authors' contributions

Oscar H. Del Brutto – study design, imaging reading, drafting the manuscript; Robertino M. Mera – statistical analyses; Mauricio Zambrano – data collection and analysis; Julio Lamaz – imaging reading, revising the manuscript for intellectual content; Victor J. Del Brutto – data collection and analysis, revising the manuscript for intellectual content; Pablo R. Castillo – study design, drafting the manuscript.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.10.023.

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